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Patentanmeldung Nr. Patent application No. Demande de brevet n°

02076350.4

PRIORITY DOCUMENT

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Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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R C van Dijk

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
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Non steroidal progesterone receptor modulators

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Non steroidal progesterone receptor modulators

The present invention relates to progesterone receptor modulating compounds as well as to the use of these compounds in therapy.

Intracellular receptors are a class of structurally related proteins involved in the regulation of gene proteins. Steroid receptors are a subset of these receptors, including the progesterone receptor (PR), androgen receptor (AR), estrogen receptor (ER), glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). Regulation of a gene by such factors requires the intracellular receptor and a corresponding ligand which has the ability to selectively bind to the receptor in a way that affects gene transcription.

Progesterone receptor modulators (progestagens) are known to play an important role in the health of women. The natural ligand for the PR receptor is the steroid hormone progesterone, but synthetic compounds have been made which may also serve as ligands (see e.g. Jones et al U.S., Patent No. 5,688,810).

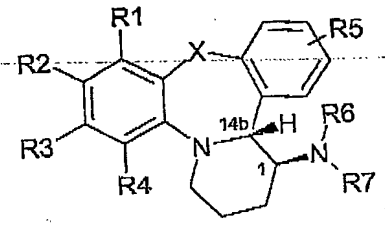
Progestagens are currently widely used for hormonal contraception and in HRT. Other important clinical applications of progestagens are treatment of gynaecological disorders (*e.g.* endometriosis, dysmenorrhea, dysfunctional uterine bleeding, severe premenstrual syndrome), breast cancer and luteal support during IVF. PR agonists are used in birth control formulations, whereas PR antagonists may be used in contraception, hormone dependent cancers, hormone displacement therapy, endometriosis etc.

The current steroidal progestagens have been proven to be quite save and are well tolerated. Sometimes, however, side effects (*e.g.* breast tenderness, headaches, depression, and weight gain) have been reported that are attributed to these steroidal progestagens either in combination with estrogenic compounds or not.

Steroidal ligands for one receptor often show cross-reactivity with other steroidal receptors. Many progestagens also bind *e.g.* to the glucocorticoid receptor. Non-steroidal progestagens have no molecular structural similarity with steroids and therefore one might also expect differences in physicochemical properties, pharmacokinetics (PK) parameters, tissue distribution (*e.g.* CNS versus peripheral) and more importantly non-steroidal progestagens may show no/less cross-reactivity to other steroid receptors. Therefore, non-steroidal progestagens will score differently in this respect.

The present invention provides non-steroidal compounds that modulate progesterone receptor activity. More particularly, the present invention provides high affinity non-steroidal compounds which are agonists, partial agonists or antagonists of the

progesterone receptor. Preferably these compounds are highly specific for the progesterone receptor. According to the present invention compounds are provided having a general formula I, or prodrug thereof, or a pharmaceutically acceptable salt of either,



Formula I

wherein

R1, R3, R4 and R5 independently can be selected from H, halogen, (1-4C)alkyl, OH, O(1-4C)alkyl, S(1-4C)alkyl or OC(O)(1-4C)alkyl,

R2 is H, halogen, NO_2, NR11R12, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, OH, O(1-4C)alkyl, S(1-4C)alkyl or OC(O)(1-4C)alkyl,

R6 is H, C(Y)R15, C(O)OR16, C(S)NR17 or (1-6C)alkyl,

R7 is H or (1-4C)alkyl, (2-4C)alkenyl or (2-4C)alkynyl, all optionally substituted with one or more halogen atoms,

R11 and R12 independently can be selected from H, (1-4C)alkyl, (2-4C)alkenyl or (2-4C)alkynyl, (1-6C)alkoxycarbonyl, (1-4C)alkylsulfonyl, (6-10C)arylsulfonyl,

R15 is H or (1-6C)alkyl, (2-4C)alkenyl or (2-4C)alkynyl , (6-10C)aryl, 1,4-bisaryl, amino (1-4C)alkyl, hydroxy(1-4C)alkyl, carboxy(1-4C)alkyl, all optionally substituted with one or more halogen atoms,

R16 is (1-6C)alkyl, optionally substituted with one or more halogen atoms,

R17 is (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl or (3-6C)cycloalkyl, all optionally substituted with one or more halogen atoms,

X=O, S, CH2 or NR18,

Y=O, S, or NH and

R18 is H or (1-4C)alkyl.

The term (1-4C)alkyl as used in the definition of the invention means a branched or unbranched alkyl group having 1-4 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl and tert-butyl.

The term halogen means fluorine, chlorine, bromine or iodine.

The term (1-6C)alkoxy means an alkoxy group having 1-6 carbon atoms, the alkyl moiety having the same meaning as previously defined. (1-2C)Alkoxy groups are preferred.

The term (1-6C)alkoxycarbonyl means an alkoxycarbonyl group, the alkoxy group of which contains 1-6 carbon atoms and has the same meaning as previously defined. (1-4C)Alkoxycarbonyl groups are preferred.

The term (1-4C)alkylsulfonyl means an alkylsulfonyl group, the alkyl group of which contains 1-4 carbon atoms and has the same meaning as previously defined. (1-2C)Alkylsulfonyl groups are preferred.

The term (6-10C)aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl or indenyl, which may optionally be substituted with one or more substituents selected from hydroxy, amino, halogen, nitro, trifluoromethyl, cyano or (1-4C)alkyl, the alkyl moiety having the same meaning as previously defined. The preferred aromatic hydrocarbon group is phenyl.

The term (6-10)arylsulfonyl means an arylsulfonyl group, the aryl group of which contains 6-10 carbon atoms and has the same meaning as previously defined. Phenylsulfonyl is preferred.

The term (2-4C)alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms, such as ethenyl and 2-butenyl.

The term (2-4C)alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, such as ethynyl and propynyl.

The term (1-6C)alkyl as used in the definition means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl and hexyl. (1-5C)Alkyl groups are preferred, (1-4C)alkyl being the most preferred.

The term amino(1-4C)alkyl means an aminoalkyl group, the alkyl group of which contains 1-4 carbon atoms and has the same meaning as previously defined. Amino(1-2C)alkyl groups are preferred.

The term hydroxy(1-4C)alkyl means a hydroxyoalkyl group, the alkyl group of which contains 1-4 carbon atoms and has the same meaning as previously defined. Hydroxy(1-2C)alkyl groups are preferred.

The term 1,4-bisaryl means two phenyl groups in which the second phenyl group is connected to the 4-position of the first phenyl group.

The term carboxy(1-4C)alkyl means a carboxyalkyl group, the alkyl group of which contains 1-4 carbon atoms and has the same meaning as previously defined. Carboxy(1-2C)alkyl groups are preferred.

The term (3-6C)cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term pharmaceutically acceptable salt represents those salts which are, within the scope of medical judgement, suitable for use in contact for the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. They may be obtained during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable mineral acid such as hydrochloric acid, phosphoric acid, or sulfuric acid, or with an organic acid such as for example ascorbic acid, citric acid, tartaric acid, lactic acid, maleic acid, malonic acid, fumaric acid, glycolic acid, succinic acid, propionic acid, acetic acid, methanesulfonic acid, and the like. The acid function can be reacted with an organic or a mineral base, like sodium hydroxide, potassium hydroxide or lithium hydroxide.

Prodrugs represent compounds which are rapidly transformed in vivo to the parent compound of the above formula, for example by hydrolysis in blood.

Stereochemical isomers; preferred is absolute stereochemistry 1S, 14bR.

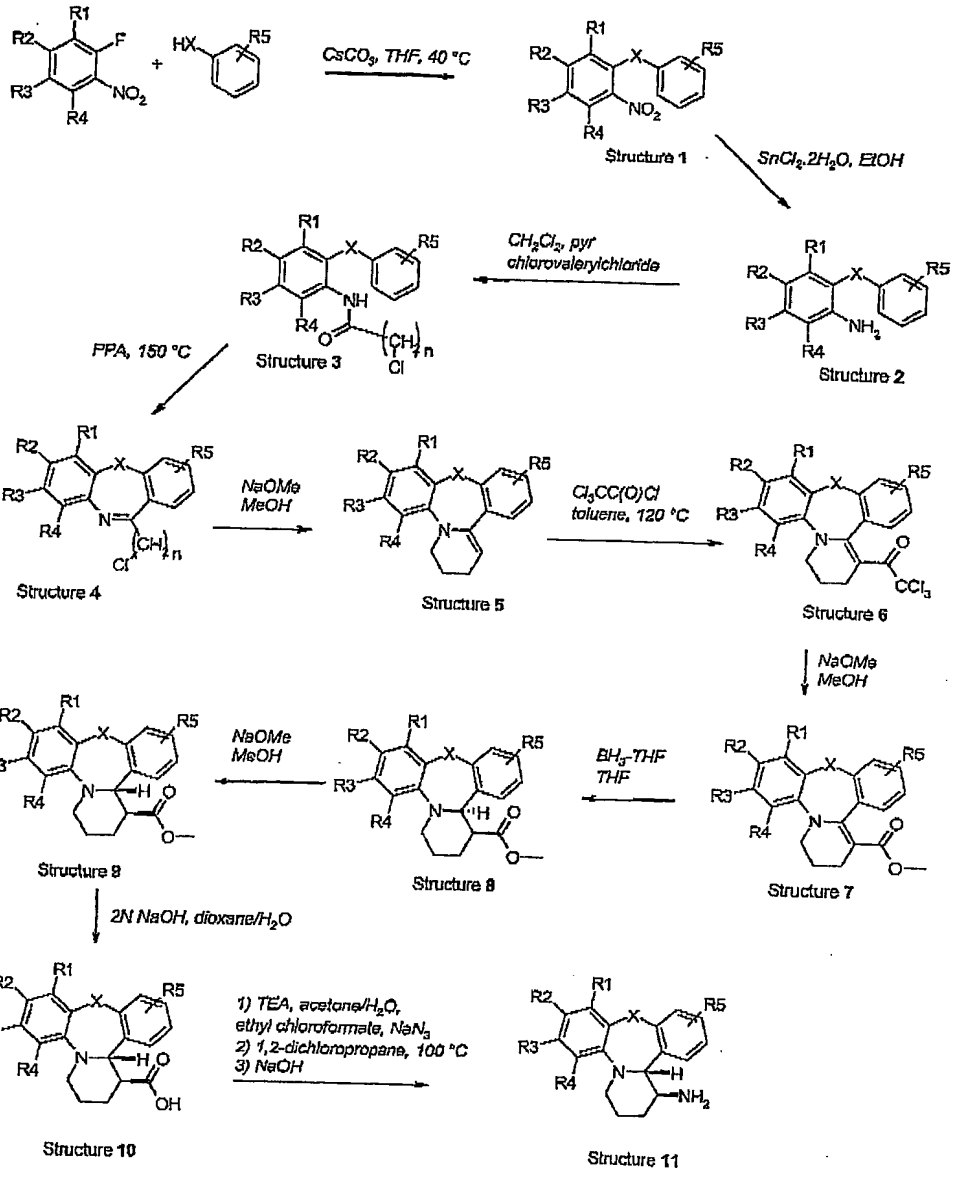
Preferred compounds are those compounds wherein R2 is H, halogen, NO_2, NR11R12 and R11 and R12 independently can be selected from H, (1-6C)alkoxycarbonyl, (1-4C)alkylsulfonyl or (6-10C)arylsulfonyl.

Particularly preferred are the compounds according to formula I wherein R1 and R5 are H and R3 and R4 are selected from H or halogen.

X preferably is O, S or CH_2, more preferably O or CH_2. Other interesting compounds are those compounds wherein R6 is H or C(Y)R15 and R15 is H or (1-4C)alkyl, preferably (1-2C)alkyl, the alkyl groups optionally substituted with one or more halogen atoms.

Also preferred are compounds wherein R2 is H, halogen or NO_2. Most preferred at R2 is H.

Scheme I



Most preferred compounds are those compounds wherein R11 is H and R12 is (1-6C)alkoxycarbonyl, (1-4C)alkylsulfonyl or (6-10C)arylsulfonyl.

Also highly preferred are compounds wherein R2 is H, R3 is halogen, R15 is methyl, optionally substituted with 1-3 halogen atoms and Y=O or S, more particularly those

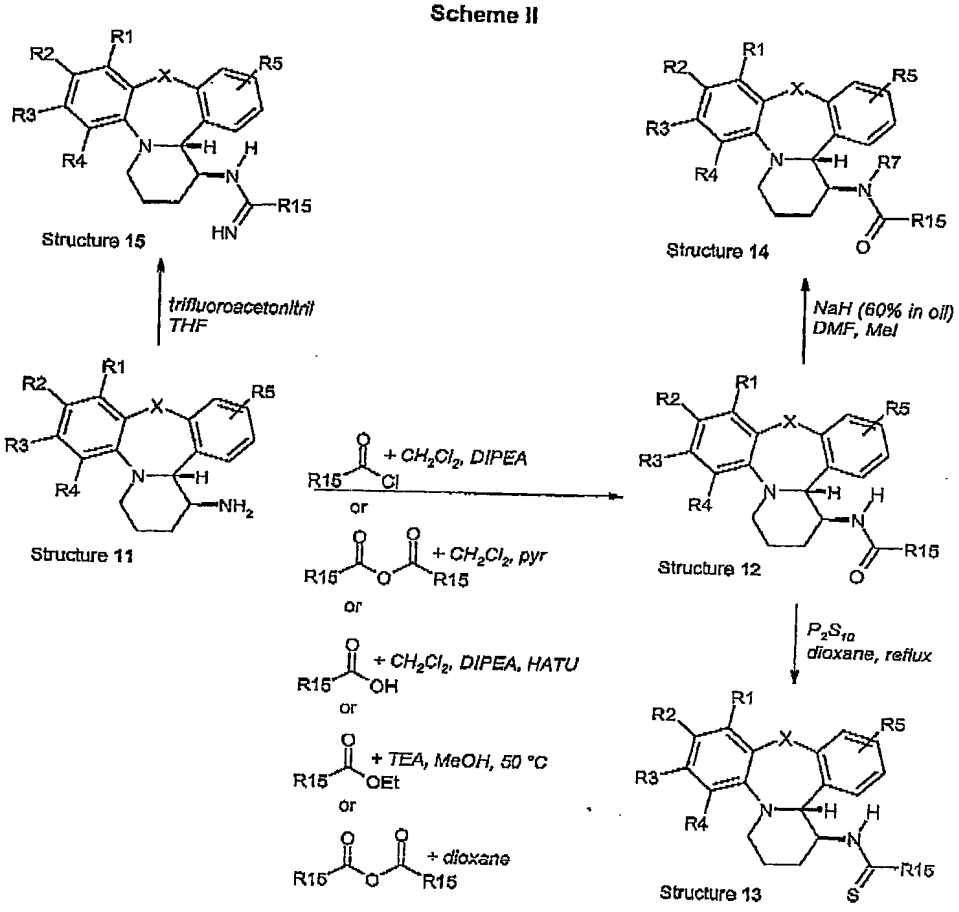
compounds wherein R4 is H and/or X=O. Compounds having some or more of the preferences identified above combined in the general formula I are highly preferred.

The sequence of steps to synthesize the compounds of the present invention are shown in Schemes **I-VI**. In each of the Schemes the R groups correspond to the substitution pattern noted in the Examples and to Formula I.

Tetracyclic templates (such as structure **11**) are constructed by routine synthetic methods as described in Scheme **I**. Nucleophilic aromatic substitution of 2-fluoro nitrophenyls with correctly substituted phenols, thiophenols or anilines provided the bisaryl structures **1**. In the case of X=CH_2, structure **1** was commercially available. Reduction of the nitro group with $SnCl_2$ yielded the aniline derivatives **2**. Acylation of the aniline functionality with 5-chlorovaleryl chloride yielded the amides **3**. Subsequent ring closure was accomplished by treatment of the amide with PPA at 150°C. Treatment of imine structures **4** with sodium methoxide resulted in an intramolecular cyclization and afforded the tetracyclic systems **5**. Reaction of the enamine functionality with trichloroacetyl chloride yielded the trichloroacetyl derivatives **6**. The trichloroacetyl functionality was transformed into methyl ester derivatives **7** on treatment with sodium methoxide. Subsequent reduction of the alkene functionality of the unsaturated carboxylates **7** with borane gave exclusively cis isomers such as structures **8**. Epimerisation to the trans isomers **9** was accomplished upon treatment of **8** with sodium methoxide. Saponification of the ester afforded the carboxylate **10** which subsequently was transformed via a classic Curtius reaction to an amine functionality resulting in the trans-1-amino--tetrahydropyrido-dibenz(ox)(othi)(di)azepine derivatives **11**. The racemic mixture was separated into its pure enantiomers via chiral HPLC (OJ column (25x0.46 cm)).

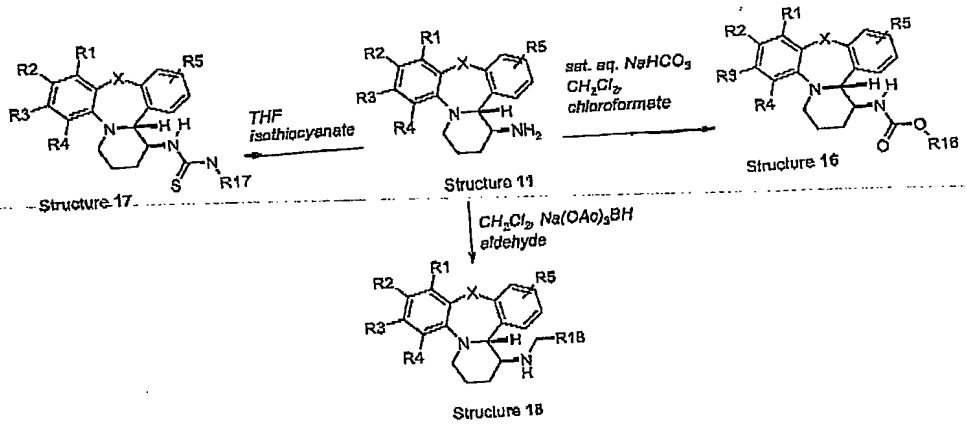
The tetracyclic compounds (**11**) are employed as starting materials in Schemes **II** and **III**. In Scheme **II** is depicted the acylation of the amine functionality of structure **11** was accomplished via various different routine synthetic methods (i.e. acid chlorides, anhydrides, carboxylic acids with coupling reagents or amidation). The resulting amide structures **12** were target of subsequent modification. Treatment of the amides such as structure **12** with phosphorous pentasulfide afforded the thioamides **13**. Alkylation of the amide in **12** with alkylating agents in the presence of sodium hydride afforded structures **14**. Structures **15** have been prepared via amidine formation of the amine functionality of **11** by treatment with nitrile derivatives such as trifluoroacetonitrile.

Scheme II



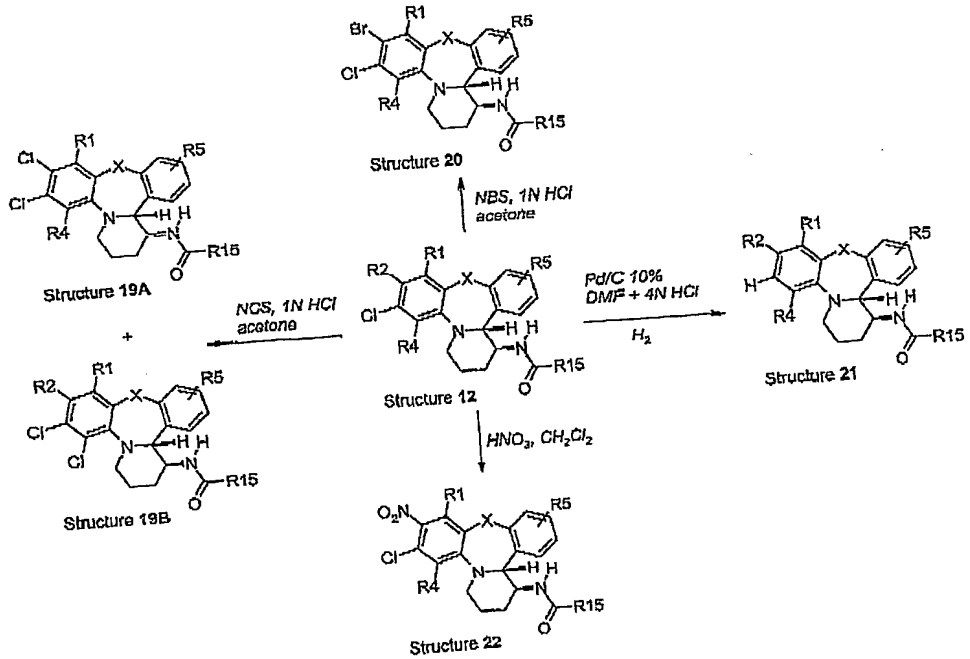
Scheme III describes the formation of the urethane structures **16** starting from **11** via reaction with chloroformates in the presence of sodium bicarbonate. Treatment of structure **11** with isothiocyanates afforded the thiourea derivatives **17**. Reductive alkylation of the amine functionality in structure **11** with aldehydes in the presence of sodium triacetoxyborohydride afforded structures **18**.

Scheme III



Direct electrophilic aromatic substitutions on core structures afforded various alternative aromatic substituted derivatives (Scheme **IV-V**).

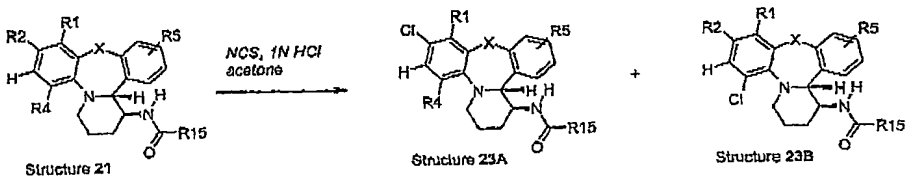
Scheme IV



In Scheme IV is described the chlorination of **12** with N-chlorosuccinimide in the presence of a catalytic amount of HCl; this resulted in the formation of the two different substituted structures **19A** and **19B**, which were easily separated. In contrast bromination of 12 with N-bromosuccinimide under identical conditions yielded only the compound with structure **20**. Reductive dehalogenation of the chloro compound (**12**) was achieved by treatment with hydrogen in the presence of Pd/C and HCl to yield the hydro derivative **21**. Nitration of structures **12** with nitric acid gave completely selective the mono substituted derivative **22**.

Direct chlorination on structure **21** (Scheme V) with N-chlorosuccinimide afforded the two regioisomers **23A** and **23B**.Two compounds which were easily separated by chromatographical methods.

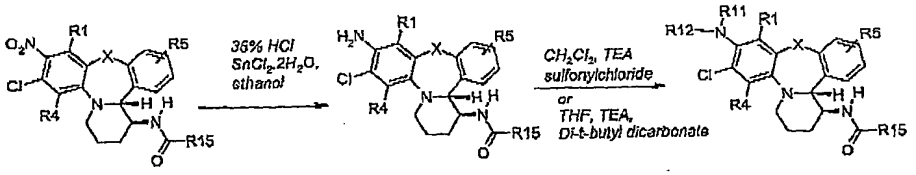
Scheme V



Structure 21 Structure 23A Structure 23B

In Scheme **VI** reduction of the nitro functionality of structures such as **22** with $SnCl_2.2H_2O$ in ethanol gave the aniline derivatives **24**. Sulfonation or acylation of this aniline functionality afforded the substituted compounds such as structure **25**,

Scheme VI



Structure 22 Structure 24 Structure 25

Methods to determine receptor binding as well as *in vitro* and *in vivo* assays to determine biological activity of the compounds are well known. In general, expressed receptor is treated with the compound to be tested and binding or stimulation or inhibition of a functional response is measured.

To measure a functional response, isolated DNA encoding the progesterone receptor gene, preferably the human receptor, is expressed in suitable host cells. Such a cell might be the Chinese Hamster Ovary (CHO) cell, but other cells are also suitable. Preferably the cells are of mammalian origin.

Methods to construct recombinant progesterone receptor-expressing cell lines are well known in the art (Sambrook et al., Molecular Cloning: a Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, latest edition). Expression of receptor is attained by expression of the DNA encoding the desired protein. Techniques for site directed mutagenesis, ligation of additional sequences, PCR, and construction of suitable expression systems are all, by now, well known in the art. Portions or all of the DNA encoding the desired protein can be constructed synthetically using standard solid phase techniques, preferably to include restriction sites for ease of ligation. Suitable control elements for transcription and translation of the included coding sequence can be provided to the DNA coding sequences. As is well known, expression systems are now available which are compatible with a wide variety of hosts, including prokaryotic hosts such as bacteria and eukaryotic hosts such as yeast, plant cells, insect cells, mammalian cells, avian cells and the like.

Cells expressing the receptor are then contacted with the test compound to observe binding, or stimulation or inhibition of a functional response.

Alternatively isolated cytosol containing the expressed receptor may be used to measure binding of compound.

For measurement of binding radioactive or fluorescence labelled compounds may be used. As reference compound the native hormone, or other compounds binding to the receptor, can be used. As an alternative, also competition binding assays can be performed.

Another assay involves screening for progesterone receptor agonist compounds by determining regulation of receptor mediated natural target gene mRNA, i.e. genes regulated by the receptor through binding of the receptor in the promoter region of the gene. The levels of target gene mRNA will be reduced or increased, depending on the inhibitory or stimulating effect of the test compound upon binding to the receptor.

In addition to direct measurement of mRNA levels in the exposed cells, cells can be used which in addition to transfection with receptor encoding DNA are also transfected with a second DNA encoding a reporter gene the expression of which responds to binding of the receptor towards responsive elements in the promoter of the particular reporter gene. Such responsive elements might be classical hormone responsive elements, well known in the art and described in Beato, M, Chalepakis, G, Schauer, M, Slater, EP (1989) J. Steroid Biochem. 5:737-47 or might be constructed in such a way that they are connected to novel responsive elements. In general, reporter gene

expression might be controlled by any response element reacting to progesterone receptor binding. Suitable reporter genes are e.g. LacZ, alkaline phosphatase, firefly luciferase and green fluorescence protein.

For selecting active agonist compounds on the progesterone receptor, testing at 10^{-5} M must result in an activity of more than 30% of the maximal activity when Org 2058 is used as a reference. For selecting antagonist compounds on the progesterone receptor, testing at 10-5M must result in an activity of more than 10% of the maximal activity when Org31710 is used as a reference. Another criterion might be the EC_{50} value, which must be $< 10^{-5}$ M, preferably $< 10^{-7}$ M.

The skilled artisan will recognize that desirable EC_{50} values are dependent on the compound tested. For example, a compound with an EC_{50}, which is less than 10^{-5} M is, generally, considered a candidate for drug selection. Preferably this value is lower than 10^{-7} M. However, a compound which has a higher EC_{50}, but is selective for the particular receptor, may be even a better candidate.

Basically any transactivation assay in mammalian cells (cell line or primary culture), that can yield information about the possible receptor activation can be used for the purpose of selecting potent ligands. The added value of using several cell systems, with cells originating from different organs, will be that information on the potential tissue specificity in action of the ligands is gained. Examples of cells frequently used to this end are, besides CHO cells, a.o. T47D cells, MCF7 cells, ECC-1 cells, HeLa cells, primary cultures of endometrial cells and pituitary cells.

The invention further resides in a pharmaceutical composition comprising a compound or a salt thereof having the general formula I.

Thus, the compounds according to the invention can be used in therapy.

The compounds of the present invention can be applied clinically in those regimens where progestagens are used.

The invention therefore resides in the use of a the compounds having the general formula I for the manufacture of a medicament for modulating progesterone receptor mediated health conditions in women, more in particular hormone dependent cancers such as breast, ovary and uterus cancer; endometriosis and fertility control. The invention also relates to a treatment of the above identified conditions by administering the compounds of the invention.

Suitable administration routes for the compounds of formula I or pharmaceutically acceptable salts thereof, also referred to herein as the active ingredient are intramuscular injections, subcutaneous injections, intravenous injections or

intraperitoneal injections, oral and intranasal administration. Preferably, the compounds may be administered orally. The exact dose and regimen of administration of the active ingredient, or a pharmaceutical composition thereof, will necessarily be dependent upon the therapeutic effect to be achieved (e.g. treatment of infertility; contraception, endometriosis) and may vary with the particular compound, the route of administration, and the age and condition of the individual subject to whom the medicament is to be administered.

In general, parenteral administration requires lower dosages than other methods of administration which are more dependent upon adsorption. However, a dosage for humans preferably contains 0.0001-25 mg per kg body weight. The desired dose may be presented as one dose or as multiple subdoses administered at appropriate intervals throughout the day, or, in case of female recipients, as doses to be administered at appropriate daily intervals throughout the menstrual cycle. The dosage as well as the regimen of administration may differ between a female and a male recipient.

The present invention thus also relates to pharmaceutical compositions comprising a compound according to formula I in admixture with pharmaceutically acceptable auxiliaries, and optionally other therapeutic agents. The auxiliaries must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

Pharmaceutical compositions include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The compositions may be prepared by any method well known in the art of pharmacy, for example, using methods such as those described in Gennaro *et al.*, Remington's Pharmaceutical Sciences (18th ed., Mack Publishing company, 1990, see especially Part 8: *Pharmaceutical Preparations and Their Manufacture*).

Such methods include the step of bringing in association the active ingredient with any auxiliary agent. The auxiliary agent(s), also named accessory ingredients, include those conventional in the art (Gennaro, *supra*), such as, fillers, binders, diluents, disintegrants, lubricants, colorants, flavouring agents and wetting agents.

Pharmaceutical compositions suitable for oral administration may be presented as discrete dosage units such as pills, tablets or capsules, or as a powder or granules, or as a solution or suspension. The active ingredient may also be presented as a bolus or paste. The compositions can further be processed into a suppository or enema for rectal administration.

The invention further includes a pharmaceutical composition, as hereinbefore described, in combination with packaging material, including instructions for the use of the composition for the use as hereinbefore described.

For parenteral administration, suitable compositions include aqueous and non-aqueous sterile injection. The compositions may be presented in unit-dose or multi-dose containers, for example sealed vials and ampoules, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of sterile liquid carrier, for example, water prior to use.

Compositions, or formulations, suitable for administration by nasal inhalation include fine dusts or mists which may be generated by means of metered dose pressurized aerosols, nebulisers or insufflators.

The derivatives of the invention can also be administered in the form of devices, consisting of a core of active material, encased by a release rate-regulating membrane. Such implants are to be applied subcutaneously or locally, and will release the active ingredient at an approximately constant rate over relatively large periods of time, for instance from weeks to years. Methods for the preparation of implantable pharmaceutical devices as such are known in the art, for example as described in European Patent 0,303,306 (AKZO N.V.).

The invention is illustrated by the following examples.

Examples

Example 1

trans-1-Amino-7-fluoro-2,3,4,14b-tetrahydro-1H- dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine (Structure 11 of Scheme I, where R1 = H, R2 = H, R3 = F, R4 = H, R5 = H, R6 = H, R7 = H, X = O)

5-Fluoro-2-phenoxynitrobenzene

Cs_2CO_3 (12.1 g, 62.9 mmol) was added to a solution of phenol (5.9 g, 62.9 mmol) in 400 mL THF under N_2. After stirring for 15 min. 2,5-difluoronitrobenzene (6.82 mL, 62.9 mmol) in 50 mL of THF was added. The resulting mixture was heated to 40 °C for 25 h. Reaction was followed by HPLC to detect disappearance of 2,5-difluoronitrobenzene. Water and ethyl acetate were added, followed by extraction with ethyl acetate (2x). The combined organic layers were successively washed with saturated aq. sodium bicarbonate (3x), water and brine, dried (Na_2SO_4) and evaporated. The crude compound was chromatographed on silica to remove excess of phenol. Elution with toluene/ethyl acetate 95:5 gave the title compound (12.6 g, 86%). Data: (m/z) = 234 $(M+H)^+$.

5-Fluoro-2-phenoxyaniline

General Method 1: Reduction of a nitro compound of Structure 1 to an aniline of Structure 2.

$SnCl_2.2H_2O$ (88.0 g, 390 mmol) was added to a solution of 5-Fluoro-2-phenoxynitrobenzene (22.3 g, 95.7 mmol) in 450 mL of ethanol under N_2. The resulting mixture was stirred at 40 °C for 30 min. and additionally under cooling for 2 h. Ethanol was removed by evaporation under reduced pressure and 300 mL of ethyl acetate was added. The organic layer was washed with water and cold 1N NaOH. The emulsion was filtered over decalite, washed with water,extracted with ethyl acetate, dried (Na_2SO4), and evaporated to give the crude compound as a dark brown oil (19.6 g, 100%). Data: (m/z) = 204 $(M+H)^+$.

5-Chloro-N-(5-fluoro-2-phenoxyphenyl)pentanamide

General Method 2: Acylation of an aniline of Structure 2 to an amide of Structure 3.

A solution of 5-chloropentanoyl chloride (13.0 mL, 100 mmol) in 13 mL CH_2Cl_2 was added in 30 minutes to a solution of 5-fluoro-2-phenoxyaniline (19.6 g, 95.7 mmol) in 88 mL of CH_2Cl_2 and 7 mL pyridine at <25 °C. After the mixture had been stirred for 1 h at room temperature 100 mL of ice-water was added at 0 °C. After 18 h stirring at room temperature the two layers were separated. The organic layer was washed with cold 2N NaOH and water, dried (Na_2SO4) and evaporated to give the crude compound as a brown oil (31.0 g, 100%). Data: (m/z) = 322 $(M+H)^+$.

8-Fluoro-11-(4-chlorobutyl)dibenz[*b,f*][1,4]oxazepine

General Method 3: Ring closure of an amide of Structure 3 to an imine of Structure 4.

PPA (190 g, 84%) was added to a solution of 5-chloro-N-(5-fluoro-2-phenoxyphenyl)pentanamide (31.0 g, 95.7 mmol). The resulting mixture was stirred at 150 °C for 2.5 h and additionally cooled to 50 °C. 500 mL of ethyl acetate and 300 mL of ice-water were added. The mixture was stirred for 1 h. The organic layer was washed with cold 1N NaOH and water, dried (Na_2SO_4) and evaporated to give the crude compound as a black oil (26.3 g, 90%). Data: (m/z) = 304 $(M+H)^+$.

7-Fluoro-3,4-dihydro-2H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine

General Method 4: Ring closure of an imine of Structure 4 to a tetracycle of Structure 5.

A solution of 8-fluoro-11-(4-chlorobutyl)dibenz[*b,f*][1,4]oxazepine (26.3 g, 86.6 mmol) in 45 mL of methanol was added to a solution of sodium methoxide (9.6 g, 177 mmol) in 115 mL of methanol under N_2. The resulting mixture was heated to reflux for 5 h, cooled to room temperature and stirred overnight. Water and CH_2Cl_2 were added and the mixture was poured into 500 mL of water and extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4) and evaporated, and the crude

compound was chromatographed on silica. Elution with toluene gave the title compound as a brown oil (16.5 g, 77%). Data: (m/z) = 268 $(M+H)^+$.

7-Fluoro-1-(trichloroacetyl)-3,4-dihydro-2H-*d*]dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine

General Method 5: Conversion of an enamine of Structure **5** to a trichloroacetyl derivative of structure **6**.

Trichloroacetyl chloride (8.75 mL, 78.5 mmol) was added to a solution of 7-fluoro-3,4-dihydro-2H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine (16.5 g, 61.9 mmol) in 125 mL of toluene under N_2. After stirring for 15 min. triethylamine (7.7 mL) was added over 15 min. The resulting brown suspension was heated to 120 °C for 75 min. After cooling to 5 °C 100 mL of ice-water was added. After stirring for 1 h the mixture was poured into 500 mL water and extracted with ethyl acetate. The organic layer was washed with cold saturated aq. sodium bicarbonate and water, dried (Na_2SO_4) and evaporated to give the crude compound as a black foam (19.1 g, 75%). Data: (m/z) = 412 $(M+H)^+$.

Methyl 7-fluoro-3,4-dihydro-2H-*d*]dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-carboxylate

General Method 6: Conversion of a trichloroacetyl compound of structure **6** to a methyl ester of structure **7**.

A solution of sodium methoxide (7.64 g, 141.6 mmol) in 60 mL methanol was added to a suspension of 7-Fluoro-1-(trichloroacetyl)-3,4-dihydro-2H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine (19.1 g, 46.4 mmol) in 60 mL of methanol. The resulting mixture was stirred for 30 min. at room temperature and heated to reflux for 1 h. After cooling to room temperature the mixture was poured into 700 mL of ice-water and extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to give the title compound as a black foam (13.9 g, 92%). Data: (m/z) = 326 $(M+H)^+$.

Methyl cis-7-fluoro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*][pyrido[1,2-*d*][1,4]oxazepine-1-carboxylate

General Method 7: Reduction of an unsaturated carboxylate of Structure **7** to a saturated carboxylate of Structure **8**.

BH_3-THF complex (1M, 40 mL, 40.0 mmol) was added in 45 min. to a solution of methyl 7-fluoro-3,4-dihydro-2H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-carboxylate

d] (14.0 g, 42.8 mmol) in 84 mL of THF under N2 (T < 5 °C). The resulting mixture was stirred for 105 min. at 20 °C. After cooling to 0 °C 20 mL of acetic acid was added in 2 h. The reaction mixture was poured into 500 mL of ice-water, extracted with CH2Cl2, washed with water, dried (Na_2SO_4) and evaporated. The crude product was chromatographed on silica. Elution with heptane/ethyl acetate 7:3 gave the title compound as a light brown foam (10.0 g, 71%). Data: (m/z) = 328 $(M+H)^+$.

Methyl trans-7-fluoro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-carboxylate

General Method 8: Epimerisation of cis-carboxylate of Structure **8** to a trans-carboxylate of Structure **9**.

Sodium methoxide (1.00 g, 1.85 mol) was added to a suspension of methyl cis-7-fluoro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*][pyrido[1,2-*d*][1,4]oxazepine-1-carboxylate d] (10.0 g, 30.6 mmol) in 100 mL of methanol under N_2. The resulting mixture was heated to reflux for 4.5 h. After cooling the clear brown solution was poured into 700 mL of ice-water and extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to give the title compound (9.1 g, 91%). Data: (m/z) = 328 $(M+H)^+$.

trans-3-Fluoro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-carboxylic acid

General Method 9: Saponification of a carboxylate of Structure **9** to a carboxylic acid of Structure **10**.

65 mL of 2N NaOH was added to a solution of methyl trans-7-fluoro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-carboxylate d] (9.10 g, 27.8 mmol) in 280 mL of dioxane and 110 mL of water. The resulting mixture was heated to 70 °C for 2 h. The cooled mixture was poured into 1.5 L of ice-water and 100 mL of 2N HCl and extracted with CH_2Cl_2 (3x). The organic layer was washed with water, dried (Na_2SO4) and evaporated. Crystallisation from CH2Cl2/ether 1:3 gave the title compound (5.3 g, 61%). Data: (m/z) = 314 $(M+H)^+$.

trans-7-Fluoro-2,3,4,14b-tetrahydro-1H-d]-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (Structure **11** of Scheme **1**, where R1 = H, R2 = H, R3 = F, R4 = H, R5 = H, R6 = H, R7 = H, X = O)

General Method 10: Amination of carboxylic acid of Structure **10** to an amine of Structure **11**.

2.60 mL of triethylamine was added in 5 minutes at 0 °C under N_2 to a suspension of trans-7-fluoro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-carboxylic acid (4.0 g, 12.8 mmol) in 30 mL of acetone and 1 mL of water. Additionally 1.80 mL of ethyl chloroformate was added and the mixture was stirred at 0 °C for 30 min. Sodium azide (1.65 g, 26.3 mmol) in 8 mL of water was added to the resulting emulsion and stirring was continued for 2.5 h at 0 °C. The mixture was poured into 500 mL of water and extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO4) and evaporated to give the crude compound. The crude compound was dissolved in 90 mL of 1,2-dichloropropane and heated to 100 °C for 4 h. The mixture was then evaporated under reduced pressure. The residue was dissolved in

45 mL methoxyethanol. A solution of sodium hydroxide (2.72 g, 84.7 mmol) in 6 mL of water was added. The resulting mixture was heated to 120 °C for 2.5 h after which it was cooled and poured into 400 mL of ice-water. The water layer was extracted with CH_2Cl_2 and the organic layer was washed with water, dried (Na_2SO4), evaporated and chromatographed on alumina. Elution with toluene/ethyl acetate 3:7 gave the title compound as a brown oil (1.45 g, 34%). Data: (m/z) = 285 $(M+H)^+$.

Example 2

trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepine-1-amine (Structure **11** of Scheme **I**, where R1 = H, R2 = H, R3 = Cl, R4 = H, R5 = H, R6 = H, R7 = H, X = S)

5-Chloro-2-(phenylthio)aniline

This compound was prepared by General Method 1 at room temperature to afford 5-chloro-2-(phenylthio)aniline (6.8 g, 77%). Data: (m/z) = 236 $(M+H)^+$.

5-Chloro-N-[5-chloro-2-(phenylthio)phenyl]pentanamide

This compound was prepared by General Method 2 to afford 5-chloro-N-[5-chloro-2-(phenylthio)phenyl]pentanamide (11.0 g, 100%). Data: (m/z) = 354 $(M+H)^+$.

8-Chloro-11-(4-chlorobutyl)dibenzo[*b,f*][1,4]thiazepine

This compound was prepared by General Method 3 to afford 8-chloro-11-(4-chlorobutyl)dibenzo[*b,f*][1,4]thiazepine as a black tar (4.0 g, 45%). Data: (m/z) = 338 $(M+H)^+$.

7-Chloro-3,4-dihydro-2H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepine

This compound was prepared by General Method 4, followed by chromatography on silica. Elution with toluene gave 7-chloro-3,4-dihydro-2H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepine as a red-brown oil (1.2 g, 47%). Data: (m/z) = 300 $(M+H)^+$.

7-Chloro-1-(trichloroacetyl)-3,4-dihydro-2H- dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepine

This compound was prepared by General Method 5 to afford 7-chloro-1-(trichloroacetyl)-3,4-dihydro-2H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepine as a black tar (1.6 g, 93%). Data: (m/z) = 446 $(M+H)^+$.

Methyl 7-chloro-3,4-dihydro-2H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepine-1-carboxylate

This compound was prepared by General Method 6 to afford methyl 7-chloro-3,4-dihydro-2H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepine-1-carboxylate as a black foam (1.2 g, 94%).

Methyl cis-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepine-1-carboxylate

This compound was prepared by General Method 7 to afford methyl cis-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepine-1-carboxylate as a brown foam (1.0 g, 100%). Data: (m/z) = 360 $(M+H)^+$.

Methyl trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepine-1-carboxylate

This compound was prepared by General Method 8 to afford methyl trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepine-1-carboxylate (0.77 g, 73%). Data: (m/z) = 360 $(M+H)^+$.

trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepine-1-carboxylic acid

This compound was prepared by General Method 9 to afford trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepine-1-carboxylic acid (0.24 g, 32%). Data: (m/z) = 346 $(M+H)^+$.

trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepine-1-amine (Structure 11 of Scheme I, where R1 = H, R2 = H, R3 = Cl, R4 = H, R5 = H, R6 = H, R7 = H, X = S)

This compound was prepared by General Method 10 to afford trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepine-1-amine as a brown solid (165 mg, 75%). Data: (m/z) = 317 $(M+H)^+$.

Example 3

trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (Structure **11** of Scheme I, where R1 = H, R2 = H, R3 = Cl, R4 = H, R5 = H, , X = O)

5-Chloro-N-(5-chloro-2-phenoxyphenyl)pentanamide

This compound was prepared by General Method 2 to afford 5-chloro-N-(5-chloro-2-phenoxyphenyl)pentanamide as a brown oil (24.1 g, 100 %). Data: ^{1}H-NMR (400 MHz, $CDCl_3$) 1.83 (m, 4H), 2.40 (t, J=7.0, 2H), 3.54 (t, J=7.0, 2H), 6.76 (d, J=8.0, 1H), 6.97 (dd, J=8.0, 2.0, 1H), 6.99 (s, 1H), 7.02 (s, 1H), 7.17 (t, J=8.0, 1H, 7.37 (d, J=8.0, 1H), 7.39 (d, J=8.0, 1H), 7.72 (br, 1H), 8.54 (d, J=2.0, 1H). (m/z) = 338 $(M+H)^+$.

8-Chloro-11-(4-chlorobutyl)dibenz[*b,f*][1,4]oxazepine

This compound was prepared by General Method 3 to afford 8-chloro-11-(4-chlorobutyl)dibenz[*b,f*][1,4]oxazepine as a thick brown-greenish oil (21.6 g, 94%).

Data: ^{1}H-NMR (400 MHz, $CDCl_3$) 1.90 (m, 4H), 2.96 (t, J=8.0, 2H), 3.58 (t, J=8.0, 2H), 7.04-7.48 (7 arH). (m/z) = 320 $(M+H)^+$.

7-Chloro-3,4-dihydro-2H-dibenz[*b,f*]pyrido[1,2-*d*][1,4]oxazepine

This compound was prepared by General Method 4, followed by chromatography on alumina. Elution with toluene gave 7-chloro-3,4-dihydro-2H-dibenz[*b,f*]pyrido[1,2-*d*][1,4]oxazepine as a dark brown oil (3.92 g, 83%). Data: ^{1}H-NMR (400 MHz, CDCl3) 2.06 (dt, J=16.0, 8.0, 2H), 2.32 (m, 2H), 3.69 (t, J=8.0, 2H), 4.87 (t, J=4.0, 1H), 6.73 (dd, J=8.0, 3.0, 1H), 6.90 (d, J=3.0, 1H), 7.02 (d, J=8.0, 1H), 7.09 (m, 2H), 7.22 (m, 1H), 7.36 (dd, J=8.0, 2.0, 1H). (m/z) = 284 $(M+H)^+$.

7-Chloro-1-(trichloroacetyl)-3,4-dihydro-2H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine

This compound was prepared by General Method 5 to afford 7-chloro-1-(trichloroacetyl)-3,4-dihydro-2H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepined] as a black tar (5.70 g, >100% crude). Data: ^{1}H-NMR (400 MHz, $CDCl_3$) 2.19 (dt, J=16.0, 8.0, 2H), 2.95 (m, 2H), 3.90 (m, 2H), 6.96 (dd, J=8.0, 3.0, 1H), 7.04-7.37 (7 arH). (m/z) = 430 $(M+H)^+$.

Methyl 7-chloro-3,4-dihydro-2H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-carboxylate

This compound was prepared by General Method 6 followed by chromatography on silica. Elution with toluene/ethyl acetate 9:1 gave methyl 7-chloro-3,4-dihydro-2H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-carboxylated] (2.75 g, 65%). Data: ^{1}H-NMR (400 MHz, $CDCl_3$) 2.11 (dt, J=16.0, 8.0, 2H), 2.65 (m, 2H), 3.38 (s, 3H), 3.82 (m, 2H), 6.88 (dd, J=8.0, 3.0, 1H), 7.06 (m, 3H), 7.14 (d, J=8.0, 1H), 7.23 (dd, J=8.0, 2.0, 1H), 7.30 (dt, J=8.0, 2.0, 1H). (m/z) = 342 $(M+H)^+$.

Methyl cis-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-carboxylate

This compound was prepared by General Method 7 to afford Methyl cis-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-carboxylated] as a yellow-brown foam (10.2 g, 100%). Data: ^{1}H-NMR (400 MHz, $CDCl_3$) 2.27 (m, 4H), 3.02 (dt, J=12.0, 4.0, 1H), 3.16 (m, 2H), 3.53 (s, 3H), 5.06 br, 1H), 6.75 (dd, J=8.0, 3.0, 1H), 6.90 (d, J=3.0, 1H), 7.00 (d, J=8.0, 1H), 7.05 (dt, J=8.0, 2.0, 1H), 7.17 (dt, J=8.0, 2.0, 2H), 7.20 (dt, J=8.0, 2.0, 1H). (m/z) = 344 $(M+H)^+$.

Methyl trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-carboxylate

This compound was prepared by General Method 8 to afford Methyl trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-carboxylate

d](9.5 g, 93%). Data: (m/z) = 344 $(M+H)^+$.

trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-carboxylic acid

This compound was prepared by General Method 9. Crystallisation from CH_2Cl_2/ether 1:3 gave trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-carboxylic acidd] (3.89 g, 51%) Data: (m/z) = 302 $(M+H)^+$.

trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (Structure 11 of Scheme I, where R1 = H, R2 = H, R3 = Cl, R4 = H, R5 = H, X = O)

This compound was prepared by General Method 10. Crystallisation from ether gave trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine as an off-white solid (2.97 g, 68%). Data: (m/z) = 301 $(M+H)^+$.

Example 4

trans-7-Chloro-1,2,3,4,10,14b-hexahydro-dibenzo[*c,f*]pyrido[1,2-*a*]azepine-1-amine (Structure 11 of Scheme I, where R1 = H, R2 = H, R3 = Cl, R4 = H, R5 = H, R6 = H, R7 = H, X = CH_2)

5-Chloro-N-[5-chloro-2-(phenylmethyl)phenyl]pentanamide

This compound was prepared by General Method 2 to afford 5-chloro-N-[5-chloro-2-(phenylmethyl)phenyl]pentanamide as an off-white solid (2.90 g, 100%). Data: (m/z) = 336 $(M+H)^+$.

8-Chloro-5-(4-chlorobutyl)dibenz[*b,e*]azepine

This compound was prepared by General Method 3 to afford 8-chloro-5-(4-chlorobutyl)dibenz[*b,e*]azepine as a black tar (2.60 g, 97%). Data: (m/z) = 318 $(M+H)^+$.

7-Chloro-2,3,4,10-tetrahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepine

This compound was prepared by General Method 4, followed by chromatography on silica. Elution with toluene gave 7-chloro-2,3,4,10-tetrahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepine as a brown-orange oil (0.89 g, 39%). Data: (m/z) = 282 $(M+H)^+$.

7-Chloro-1-(trichloroacetyl)-2,3,4,10-tetrahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepine

This compound was prepared by General Method 5 to afford 7-chloro-1-(trichloroacetyl)-2,3,4,10-tetrahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepine as a dark brown foam (1.34 g, 99%).

Methyl 7-chloro-2,3,4,10-tetrahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepine-1-carboxylate

This compound was prepared by General Method 6 to afford methyl 7-chloro-2,3,4,10-tetrahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepine-1-carboxylate as a dark brown foam (1.01 g, 95%). Data: (m/z) = 340 $(M+H)^+$.

Methyl cis-7-chloro-1,2,3,4,10,14b-hexahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepine-1-carboxylate

This compound was prepared by General Method 7 to afford methyl cis-7-chloro-1,2,3,4,10,14b-hexahydrodibenzo[c,*f*]pyrido[1,2-*a*]azepine-1-carboxylate as a dark brown foam (1.00 g, 98%). Data: (m/z) = 342 $(M+H)^+$.

Methyl trans-7-chloro-1,2,3,4,10,14b-hexahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepine-1-carboxylate

This compound was prepared by General Method 8 to afford methyl trans-7-chloro-1,2,3,4,10,14b-hexahydro-dibenzo[*c,f*]pyrido[1,2-*a*]azepine-1-carboxylate (0.93 g, 93%).

trans 7-Chloro-1,2,3,4,10,14b-hexahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepine-1-carboxylic acid

This compound was prepared by General Method 9. Crystallisation from CH_2Cl_2/ether 1:3 gave trans-7-chloro-1,2,3,4,10,14b-hexahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepine-1-carboxylic acid (3.89 g, 51%) Data: (m/z) = 302 $(M+H)^+$.

trans-7-Chloro-1,2,3,4,10,14b-hexahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepine-1-amine (Structure 11 of Scheme I, where R1 = H, R2 = H, R3 = Cl, R4 = H, R5 = H, R6 = H, R7 = H, X = CH2)

This compound was prepared by General Method 10 to afford trans-7-chloro-1,2,3,4,10,14b-hexahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepine-1-amine (104 mg, 86%). Data: (m/z) = 299 $(M+H)^+$.

Example 5

2,2,2-Trifluoro-N-(trans-7-fluoro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)acetamide

(Structure **12** of Scheme **II**, where R1 = H, R2 = H, R3 = F, R4 = H, R5 = H, R15 = CF_3, X = O)

General Method 11: N-acylation of an amine of Structure **11** to a trifluoro amide of Structure **12**.

Trifluoroacetic anhydride (1 mL) was added to trans-7-fluoro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (0.6 g, 2.1 mmol) in 5 mL CH_2Cl_2 and 2 mL of pyridine. The resulting suspension was stirred for 18 h at room temperature. The brown solution was poured into 100 mL of ice-water and extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. Diethyl ether was added to the resulting solid and heated to reflux for 30 min. The residue was dissolved in CH_2Cl_2 and heated to reflux for 30 min. The precipitate was filtered off, washed with CH_2Cl_2 and dried to give 2,2,2-trifluoro-N-(trans-7-fluoro-2,3,4,14b-

tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)acetamide as an off-white solid (0.2 g, 25.6%). Data: (m/z) = 381 $(M+H)^+$.

Example 6

2,2,2-Trifluoro-N-(trans-7-fluoro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepin-1-yl)acetamide (Structure 13 of Scheme II, where R1 = H, R2 = H, R3 = Cl, R4 = H, R5 = H, R15 = CF_3, X = S)

This compound was prepared by General Method 11, followed by chromatography on silica. Elution with toluene -> toluene/ethyl acetate 95:5 followed by crystallisation from ether, which gave trifluoro-N-(trans-7-fluoro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]thiazepin-1-yl)acetamide as an off-white solid (3.0 mg, 12%). Data: (m/z) = 413 $(M+H)^+$.

Example 7

N-(trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2-2-2-trifluoroacetamide (Structure 12 of Scheme II, where R1 = H, R2 = H, R3 = Cl, R4 = H, R5 = H, R15 = CF_3, X = O)

Successively, ethyl trifluoroacetate (1.41 mL, 11.8 mmol) and triethylamine (628 L, 4.5 mmol) were added to trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (291 mg, 0.97 mmol) in 11.8 mL of methanol. The resulting mixture was heated to 50 °C for 18 h. A precipitate was formed. The mixture was evaporated under reduced pressure to remove volatile reagents and 5 mL of methanol was added. After 30 min. stirring the precipitate was filtered off, washed with diethyl ether and dried to give N-(trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide as an off-white solid (330 mg, 86%). Data: ^{1}H-NMR (400 MHz, $CDCl_3$) 1.85 (m, 2H), 2.26 (m, 1H), 3.12 (m, 1H), 3.20 (m, 1H), 3.62 (dt, J=12.0, 4.0, 1H), 4.38 (d, J=8.0, 1H), 4.68 (m, 1H), 6.76 (dd, J=8.0, 3.0, 1H), 6.93 (d, J=3.0, 1H), 7.04 (d, J=8.0, 1H), 7.08 (dt, J=8.0, 2.0, 1H), 7.17 (dd,dd, J=8.0, 2.0, 2H), 7.29 (dt, J=8.0, 2.0, 1H). (m/z) = 397 $(M+H)^+$.

Example 8

N-(trans-7-Chloro-1,2,3,4,10,14b-hexahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepin-1-yl)-2,2,2-trifluoroacetamide (Structure 12 of Scheme II, where R1 = H, R2 = H, R3 = Cl, R4 = H, R5 = H, R15 = CF_3, X = CH_2)

This compound was prepared by General Method 11, followed by chromatography on silica. Elution with toluene -> toluene/ethyl acetate 95:5 gave N-(trans-7-chloro-

1,2,3,4,10,14b-hexahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepin-1-yl)-2,2,2-trifluoroacetamide (34.0 mg, 12%). Data: (m/z) = 395 $(M+H)^+$.

Example 9

N-(trans-1,2,3,4,10,14b-Hexahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepin-1-yl)-2,2,2-trifluoroacetamide (Structure **12** of Scheme **II**, where R1 = H, R2 = H, R3 = H, R4 = H, R5 = H, R15 = CF_3, X = CH_2)

This compound was prepared by General Method 11 starting from trans-1,2,3,4,10,14b-hexahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepine-1-amine maleate, followed by chromatography on silica. Elution with toluene -> toluene/ethyl acetate 9:1 gave N-(cis-1,2,3,4,10,14b-hexahydrodibenzo[*c,f*]pyrido[1,2-*a*]azepin-1-yl)-2,2,2-trifluoroacetamide (3.6 mg, 76%). Data: (m/z) = 359 $(M+H)^+$.

Example 10

N-(trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin1-yl)acetamide (Structure **12** of Scheme II, where R1 = R2 = H, R3 = Cl, R4 = R5 = H, R6 = C(O)R15, R7 = H, R15 = CH_3, X = O)

trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine maleate (10 mg, 0.02 mmol), 50 µL of pyridine, and 25 µL of acetic anhydride in 1mL of CH_2Cl_2 were stirred for 18 h at room temperature. The mixture was washed with 5% aqueous sodium bicarbonate and H_2O, dried (Na_2SO_4) and evaporated to give N-(trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin1-yl)acetamide (9.0 mg, 65%). Data: (m/z) = 343 $(M+H)^+$.

Example 11

N-(trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2-fluoroacetamide (Structure **12** of Scheme **II**, where R1 = R2 = H, R3 = Cl, R4 = R5 = H, R15 = CH_2F, X = O)

trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (10 mg, 0.03 mmol) was dissolved in 1 mL of ethyl fluoroacetate. The resulting mixture was heated to reflux for 2 h. Evaporation followed by crystallisation from methanol gave N-(trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2-fluoroacetamide (4.7 mg, 39 %). Data: (m/z) = 361 $(M+H)^+$.

Example 12

N-(trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-4-phenylbenzamide (Structure 12 of Scheme II, where R1 = R2 = H, R3 = Cl, R4 = R5 = H, R15 = $C_6H_4C_6H_5$, X = O)

General Method 12: N-acylation of an amine of Structure **11** to an amide of Structure **12**.

DIPEA (18.6 µL, 0.14 mmol) and 4-phenylbenzoyl chloride (15.2 mg, 0.07 mmol) were added to a solution of trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine maleate (9.6 mg, 0.02 mmol) in 1 mL of CH_2Cl_2. The resulting mixture was stirred for 18 h at room temperature. The organic layer was washed with 5% aqueous sodium bicarbonate and H_2O, dried (Na_2SO_4) and evaporated. Additional chromatography on silica (elution with toluene/ethyl acetate 9:1 -> toluene/ethyl acetate 1:1) gave N-(trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-4-phenylbenzamide (4.6 mg, 44%). Data: (m/z) = 350 $(M+H)^+$.

The following amides listed in Table 1 were prepared essentially by General Method 12, using the appropriate starting materials. For Example 15 triethylamine was used instead of DIPEA and the compound was crystallised from diethyl ether.

Table 1

Ex	R1	R2	R3	R4	R5	R6	R7	R15	X	(m/z)	yield (%)
13	H	H	Cl	H	H	C(O)R15	H	CHF_2	O	379	35
14	H	H	Cl	H	H	C(O)R15	H	CH_2Cl	O	377	52
15	H	H	Cl	H	H	C(O)R15	H	CH_2Br	O	422	50

Example 16

2-Amino-N-(trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)acetamide (Structure 12 of Scheme II, where R1 = R2 = H, R3 = Cl, R4 = R5 = H, R15 = CH_2NH_2, X = O)

trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-yl)amino]carbonyl]methyl]carbamic acid 1,1-dimethylethyl ester

General Method 13: N-acylation of an amine of Structure 11 to an amide of Structure 12.

DIPEA was added (pH=9) to trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (10 mg, 0.03 mmol) in 1 mL of CH_2Cl_2

with HATU (12.5 mg, 0.03 mmol) and Boc-Gly-OH (10.3 mg, 0.03 mmol). The resulting mixture was stirred for 3 h, washed with 5% aqueous sodium bicarbonate and H_2O, dried (Na_2SO_4) and evaporated to give [[[(trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-yl)amino]carbonyl]methyl]carbamic acid 1,1-dimethylethyl ester (14.3 mg, 100%). Data: (m/z) = 405 $(M+H)^+$.

2-Amino-N-(trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)acetamide (Structure **12** of Scheme II, where R1 = R2 = H, R3 = Cl, R4 = R5 = H, R15 = CH_2NH_2, X = O)

trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-yl)amino]carbonyl]methyl]carbamic acid 1,1-dimethylethyl ester (10 mg, 0.02 mmol) in 2 mL of ethyl acetate was purged with HCl-gas at 0 °C for 2 h. The mixture was evaporated under reduced pressure to give 2-Amino-N-(trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)acetamide (9.2 mg, 100%). Data: (m/z) = 358 $(M+H)^+$.

Example 17

4-[(trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)amino]-2,2,3,3-tetrafluoro-4-oxobutanoic acid (Structure 12 of Scheme II, where R1 = R2 = H, R3 = Cl, R4 = R5 = H, R15 = $CF_2CF_2C(O)OH$, X = O)

Tetrafluorosuccinic anhydride (5.35 L, 0.05 mmol) was added to trans-7-chloro 2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (10 mg, 0.03 mmol) in 1 mL of dioxane. The resulting mixture was stirred at room temperature for 30 minutes. Dioxane was removed by evaporation under reduced pressure and ethyl acetate and 2% citric acid were added. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give 4-[(trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)amino]-2,2,3,3-tetrafluoro-4-oxobutanoic acid (10.6 mg, 51%). Data: (m/z) = 472 $(M+H)^+$.

Example 18

N-(trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)methanethioamide (Structure **13** of Scheme II, where R1 = R2 = H, R3 = Cl, R4 = R5 = H, R15 = H, X = O)

N-(trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)formamide

trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (10 mg, 0.03 mmol) was dissolved in 1 mL of ethyl formate. The resulting mixture was heated to reflux for 18 h. The cooled mixture was evaporated to give N-

(trans-7-chloro-2,3,4,14b-tetrahydro-1H--dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)formamide (12.0 mg, 100 %). Data: (m/z) = 329 $(M+H)^+$.

N-(trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)methanethioamide (Structure 13 of Scheme II, where R1 = R2 = H, R3 = Cl, R4 = R5 = H, R15 = H, X = O)

General Method 14: Sulfonylation of an amide of Structure **12** to a thioamide of Structure 13.

Phosphorus pentasulfide (5 mg, 0.01 mmol) was added to N-(trans-7-chloro2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)formamide (5 mg, 0.015 mmol) in dioxane. The resulting mixture was heated to reflux for 3 h. After evaporation under reduced pressure the crude compound was chromatographed on silica. Elution with toluene/ethyl acetate 85:15 gave N-(trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)methanethioamide (2.8 mg, 51%). Data: (m/z) = 345 $(M+H)^+$.

The following thioamides listed in Table 2 were prepared essentially by General Method 14, using the appropriate starting materials. They are referred to as examples 19 through 27.

Table 2

Ex	R1	R2	R3	R4	R5	R6	R7	R15	X	(m/z)	Yield (%)
19	H	H	Cl	H	H	C(S)R15	H	CF_3	O	413	98
20	H	H	Cl	H	H	C(S)R15	H	CF_3	CH_2	411	62
21	H	H	Cl	H	H	C(S)R15	H	CH_3	O	359	11
22	H	H	Cl	H	H	C(S)R15	H	CH_2F	O	378	63
23	H	H	Cl	H	H	C(S)R15	H	CHF_2	O	395	80
24	H	H	Cl	H	H	C(S)R15	CH_3	CF_3	O	428	49
25	H	H	H	H	H	C(S)R15	H	CF_3	O	379	24
26	H	H	Cl	Cl	H	C(S)R15	H	CF_3	O	448	47
27	H	H	Cl	H	H	C(S)R15	H	CH_2NH_2	O	374	75

EXAMPLE 28

N-(trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoro-*N*-methylacetamide (Structure **14** of Scheme II, where R1 = R2 = H, R3 = Cl, R4 = R5 = H, R7 = CH_3, R15 = CF_3, X = O)

Sodium hydride (1.6 mg, 60% in oil) was added to (trans-7-chloro-2,3,4,14b-tetrahydro-1H--dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (15 mg, 0.04 mmol) in 1 mL of DMF. After 10 minutes stirring methyl iodide (2.47 L, 0.04 mmol) was added. The resulting mixture was stirred at room temperature for 18 h. After evaporation the crude compound was purified by chromatography on silica. Elution with toluene/ethyl acetate 7:3 gave N-(trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoro-*N*-methylacetamide (14 mg, 90%). Data: (m/z) = 411 $(M+H)^+$.

Example 29

N-(trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetimidamide (Structure **15** of Scheme II, where R1 = H, R2 = H, R3 = Cl, R4 = H, R5 = H, R15 = CF_3, X = O

Trifluoroacetonitrile was added to a solution of (trans-7-chloro-2,3,4,14b-tetrahydro-1H--dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (10 mg, 0.03 mmol) in 2 mL of THF for 2 h. The mixture was stirred at room temperature for 16 hr. After evaporation the crude compound was chromatographed on silica. Elution with toluene gave N-(trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetimidamide (7.14 mg, 55%). Data: (m/z) = 396 $(M+H)^+$.

Example 30

1-(trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)carbamic acid chloromethyl ester (Structure **16** of Scheme III, where R1 = R2 = H, R3 = Cl, R4 = R5 = H, R16 = CH_2Cl, X = O)

General Method 15: N-acylation of an amine of Structure **11** to a carbamate of Structure **16**.

100 µL saturated aq. sodium bicarbonate was added to trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (9.5 mg, 0.03 mmol) and chloromethyl chloroformate (64.2 L, 0.42 mmol) in 250 µL of CH_2Cl_2. The resulting mixture was stirred at room temperature for 18 h. Additionally ethyl acetate was added and the organic layer was washed with water, dried (Na_2SO_4) and

evaporated to give 1-(trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)carbamic acid chloromethyl ester (9.9 mg, 88%). Data: (m/z) = 393 $(M+H)^+$.

Example 31

(trans-7-Chloro,2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)carbamic acid 2-bromoethyl ester (Structure **16** of Scheme III, where R1 = R2 = H, R3 = Cl, R4 = R5 = H, R16 = CH_2CH_2Br, X = O)

This compound was prepared by General Method 15 to afford (trans-7-chloro,2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)carbamic acid 2-bromoethyl ester (yield 80%). Data: (m/z) = 452 $(M+H)^+$.

Example 32

N-(trans-7-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-N'-(2-methylpropyl)thiourea (Structure **17** of Scheme III, where R1 = R2 = H, R3 = Cl, R4 = R5 = H, R17 = $CH_2CH(Me)_2$, X = O)

General Method 16: Isobutyl isothiocyanate (3.35 mg, 0.03 mmol) was added to trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (5 mg, 0.02 mmol) in 1 mL of THF. The resulting mixture was stirred at room temperature for 18 h. The mixture was evaporated under reduced pressure. Crystallisation from methanol gave N-(trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-N'-(2-methylpropyl)thiourea (1 mg, 12%). Data: (m/z) = 416 $(M+H)^+$.

The following thioureas listed in Table 3 were prepared essentially by General Method 16, using the appropriate starting materials. They are referred to as examples 33 through 35.

Table 3.

Ex	R1	R2	R3	R4	R5	R6	R7	X	R17	(m/z)	Yield(%)
33	H	H	Cl	H	H	C(S)NR17	H	O	cC_6H_{11}	442	20
34	H	H	Cl	H	H	C(S)NR17	H	O	$CH_2CH=CH_2$	400	26
35	H	H	Cl	H	H	C(S)NR17	H	O	$C(Me)_3$	416	12

Example 36

trans-N-(2-Methylpropyl)-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (Structure **18** of Scheme III, where R1 = R2 = H, R3 = Cl, R4 = R5 = H, R6 = CH_2R18, R7 = H, R18 = $CH(CH_3)_2$, X = O)

General Method 17: N-alkylation of an amine of Structure **11** to an N-alkyl of Structure **18**.

After 10 min. stirring sodium triacetoxyborohydride (11 mg, 0.05 mmol) was added to trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (10 mg, 0.03 mmol) and isobutyraldehyde (3.45 mg, 0.03 mmol) in 1 mL of CH_2Cl_2 (pH≈4). The resulting mixture was stirred at room temperature for 18 h. The mixture was evaporated and chromatographed on silica. Elution with CH_2Cl_2/methanol 8:2 gave trans-N-(2-methylpropyl)-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (13 mg, 100%). Data: (m/z) = 357 $(M+H)^+$.

Example 37

trans-N-Propyl-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (Structure **18** of Scheme III, where R1 = R2 = H, R3 = Cl, R4 = R5 = H, R18 = CH_2CH_3, X = O)

This compound was prepared by General Method 17 to afford trans-N-propyl-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-amine (10 mg, 97%). Data: (m/z) = 343 $(M+H)^+$.

Examples 38A and B

trans-6,7-Dichloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (Example 38A) (Structure **19A** of Scheme **IV**, where R1 = H, R2 = Cl, R3 = Cl, R4 = R5 = H, R15 = CF_3, X = O)

trans-7,8-Dichloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (Example 38B) (Structure **19B** of Scheme **IV**, where R1 = R2 = H, R3 = Cl, R4 = Cl, R5 = H, R15 = CF_3, X = O)

N-chlorosuccinimide (6.87 mg, 0.05 mmol) and 0.5 L 1N HCl was added to (trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (20 mg, 0.05 mmol) in 102 L of acetone. The resulting mixture was stirred at room temperature for 18 h. No reaction was observed. The reaction was repeated under the same conditions. The resulting mixture was stirred at room temperature for 1.5 h. The organic layer was washed with saturated aq. sodium bicarbonate and water, dried (Na_2SO_4) and evaporated and the crude compound was purified by prep. HPLC to give (trans-6,7-dichloro-2,3,4,14b-tetrahydro-1H-

dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (3.6 mg, 17%) and (trans-7,8-dichloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (1.6 mg, 7%). Data: (m/z) = 431 $(M+H)^+$.

Example 39

trans-8-Bromo-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (Structure **20** of Scheme **IV**, where R1 = H, R2 = Br, R3 = Cl, R4 = H, R5 = H, R6 = C(O)R15, R7 = H, R15 = CF_3, X = O)

N-bromosuccinimide (9.2 mg, 0.05 mmol) and 0.5 L 1N HCl were added to (trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (20 mg, 0.05 mmol) in 512 L of acetone. The resulting mixture was stirred at room temperature for 30 min. The mixture was diluted with ethyl acetate, washed with saturated aq. sodium bicarbonate and water, dried (Na_2SO_4) and evaporated to give (trans-8-Bromo-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide as a white solid (31 mg, 100%). Data: ^{1}H-NMR (400 MHz, $CDCl_3$) 1.85 (m, 4H), 2.27 (m, 2H), 3.20 (m, 1H), 3.64 (m, 1H), 4.44 (d, J=8.0, 1H), 4.65 (m, 1H), 6.26 (b, 1H), 7.02 (s, 1H), 7.10 (dt, J=8.0, 2.0, 1H), 7.16 (m, 2H), 7.30 (dt, J=8.0, 3.0, 1H), 7.35 (s, 1H). (m/z) = 477 $(M+H)^+$.

Example 40

trans-2,3,4,14b-Tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (Structure **21** of Scheme **IV**, where R1 = R2 = R4 = R5 = H, R15 = CF_3, X = O)

10 mg Pd/C 10% was added to a solution of (trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (100 mg, 0.25 mmol) in 5 mL of DMF. The suspension was shaken under H_2 atmosphere for 2 days. The mixture was filtered, poured into water and extracted with diethyl ether. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to give (trans-2,3,4,14b-Tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (89 mg, 98%). Data: ^{1}H-NMR (400 MHz, $CDCl_3$) 1.85 (m, 3H), 2.99 (m, 1H), 3.18 (m, 1H), 3.75 (m, 1H), 4.50 (d, J= 8, 1H), 4.72 (m, 1H), 6.62 (br, 1H), 6.84-7.30 (8 arH). (m/z) = 362 $(M+H)^+$.

Example 41

trans-7-Chloro-8-nitro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (Structure **22** of Scheme **IV**, where R1 = H, R2 = NO_2, R3 = Cl, R4 = H, R5 = H, R6 = C(O)R15, R7 = H, R15 = CF_3, X = O)

Nitric acid (50 L, 1.10 mmol) was added at 0 °C to a suspension of (trans-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (210 mg, 0.53 mmol) in 4 mL of CH_2Cl_2. After stirring the mixture was extracted with ethyl acetate and the organic layer was washed with 5% aq. sodium bicarbonate, dried (Na_2SO_4) and evaporated to give (trans-7-chloro-8-nitro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (219 mg, 90%). Data: ^{1}H-NMR (400 MHz, DMSO) 1.64-1.94 (m, 3H), 2.05 (br, 1H), 3.26 (t, J=8.0, 1H), 4.20 (d, J=8.0, 1H), 4.35 (d, J=8.0, 1H), 4.60 (dq, J=8.0, 3.0, 1H) 7.15 (m, 1H), 7.11-9.21 (6 ArH). (m/z) = 443 $(M+H)^+$.

Examples 42 A and B

trans-6-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (Example 42A) (Structure **23A** of Scheme **V**, where R1 = H, R2 = Cl, R3 = R4 = R5 = H, R15 = CF_3, X = O)

trans-8-Chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (Example 42B) (Structure **23B** of Scheme **V**, where R1 = R2 = R5 = H, R15 = CF_3, X = O)

N-chlorosuccinimide (8.52 mg, 0.06 mmol) and 0.67 L of 1N HCl were added to 1-N-(trans-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (21 mg, 0.06 mmol) in 1 mL of acetone. The resulting mixture was stirred at room temperature for 2 h. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated aq. sodium bicarbonate and evaporated. The crude compound was chromatographed on silica. Elution with heptane/ethyl acetate 8:2 gave the two compounds: (trans-6-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (9.8 mg, 41%). Data: ^{1}H-NMR (400 MHz, $CDCl_3$) 1.84 (m, 3H), 2.22 (m, 1H), 3.17 (m, 1H), 3.52 (m, 1H), 4.44 (d, J=8.0, 1H), 4.69 (m, 1H), 6.48 (br, 1H), 6.90 (d, J=8.0, 1H), 6.97 (dd, J=8.0, 3.0, 1H), 7.10 (dt, J=8.0, 2.0, 1H), 7.13 (d, J=3.0, 1H), 7.19 (d, J=8.0, 2H), 7.29 (dt, J=8.0, 2.0, 1H). (m/z) = 397 $(M+H)^+$.

The 8-chloro substituted compound containing 6,8-dichloro-substituted compound was purified by prep. HPLC to give (trans-8-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (1.2 mg, 5%). Data: ^{1}H-NMR (400 MHz, $CDCl_3$) 1.84 (m, 3H), 2.00 (m, 1H), 2.93 (dd, J=8.0, 3.0, 1H), 3.28 (dt, J=8.0, 3.0, 1H), 4.39 (s, 1H), 4.89 (m, 1H), 7.07-7.33 (7 arH), 8.07 (br, 1H). (m/z) = 397 $(M+H)^+$.

Example 43

N-(trans-7-Chloro-2,3,4,14b-tetrahydro-8-[bis(phenylsulfonyl)amino]-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (Structure 25

of Scheme VI, where R1 = H, R4 = H, R5 = H, R11 = R12 = $S(O)_2Ph$, R15 = CF_3, X = O)

N-(trans-8-Amino-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide

80 L 36% HCl and $SnCl_2.2H_2O$ (600 mg, 2.66 mmol) were added (trans-7-chloro-8-nitro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (215 mg, 0.49 mmol) in 10 mL of ethanol. The resulting mixture was stirred at 60 °C for 18 h. After cooling the mixture was evaporated and dissolved in ethyl acetate. Aq. sodium bicarbonate was added to the solution (Sn salts were formed) followed by decalite and the mixture was filtered. The filtrate was extracted with ethyl acetate and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give the title compound (194 mg, 82%). Data: (m/z) = 413 $(M+H)^+$.

Trifluoro-N-(trans-7-chloro-2,3,4,14b-tetrahydro-8-[bis(phenylsulfonyl)amino]-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)acetamide (Structure **25** of Scheme VI, where R1 = H, R4 = H, R5 = H, , R11 = R12 = $S(O)_2Ph$, R15 = CF_3, X = O)

General Method 18: N-acylation of an amine of Structure **25** to an amide of Structure **26** Benzenesulfonyl chloride (5 L, 0.04 mmol) was added under N_2 to N-(trans8-amino-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2,-trifluoroacetamide (5.0 mg, 0.01 mmol) in a mixture of 1 mL of CH_2Cl_2 and 25 L of triethylamine. The resulting mixture was stirred at 40 °C for 4 h. After cooling the mixture was evaporated and the crude compound was purified by chromatography on silica. Elution with toluene/ethyl acetate 1:0->0:1 (gradient) gave N-(trans-7-chloro-2,3,4,14b-tetrahydro-8-[bis(phenylsulfonyl)amino]-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (7.3 mg, 83%). Data: (m/z) = 692 $(M+H)^+$.

Example 44

N-(trans-7-Chloro-2,3,4,14b-tetrahydro-8-[bis(methylsulfonyl)amino]-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (Structure **25** of Scheme VI, where R1 = H, R4 = H, R5 = H, R11 = R12 = $S(O)_2CH_3$, R15 = CF_3, X = O)

This compound was prepared by General Method 18 using the appropriate starting material to afford N-(trans-7-chloro-2,3,4,14b-tetrahydro-8-[bis(methylsulfonyl)amino]-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (6.8 mg, 92%). Data: (m/z) = 568 $(M+H)^+$.

Example 45

N-(trans-7-Chloro-2,3,4,14b-tetrahydro-8-[(phenylsulfonyl)amino]-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (Structure **25** of Scheme **VI**, where R1 = H, R2 = NR11R12, R3 = Cl, R4 = H, R5 = H, R6 = C(O)R15, R7 = H, R11 = H, R12 = $S(O)_2Ph$, R15 = CF_3, X = O)

Benzenesulfonyl chloride (10 L, 0.08 mmol) was added under N_2 to N-(trans-8-amino-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (5.0 mg, 0.01 mmol) in 1 mL of CH_2Cl_2 and 2 L (1.1 eq) of triethylamine. The resulting mixture was stirred at 35 °C for 4 h. After cooling the mixture was evaporated and the crude compound was purified by chromatography on silica. Elution with toluene/ethyl acetate 1:0->0:1 (gradient) gave N-(trans-7-chloro-2,3,4,14b-tetrahydro-8-[(phenylsulfonyl)amino]-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (2.4 mg, 32%). Data: (m/z) = 552 $(M+H)^+$.

Example 46

(trans-7-Chloro-2,3,4,14b-tetrahydro-1-(2,2,2-trifluoroacetylamino)1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-8-yl)carbamic acid 1,1-dimethylethyl ester (Structure **25** of Scheme **VI**, where R1 = H, R4 = H, R5 = H, R11 = H, R12 = $C(O)OC(CH_3)_3$, R15 = CF_3, X = O)

Di-tert-butyl dicarbonate (20.55 mg, 0.09 mmol) was added at 5 °C under N_2 to N-(trans-8-amino-7-chloro-2,3,4,14b-tetrahydro-1H-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepin-1-yl)-2,2,2-trifluoroacetamide (10.8 mg, 0.03 mmol) in 1 mL of THF and 6 L (1.1 eq) of triethylamine. The resulting mixture was stirred at 50 °C for 72 h. After cooling the mixture was evaporated and chromatographed on silica. Elution with heptane/ethyl acetate 1:0->0:1 (gradient) gave the title compound (2.7 mg, 15%). Data: (m/z) = 512 $(M+H)^+$.

Example 47

Progesterone receptor-B activity in a transactivation.

The (anti-)progestagenic activity of test compounds (EC50 and intrinsic activity) is determined in an *in vitro* bioassay of Chinese hamster ovary (CHO) cells stably transfected with the human progesterone receptor-B expression plasmid and a reporter plasmid in which the MMTV-promoter is linked to the luciferase reporter gene. The cell-line is known under the name CHO-PRB-pMMTV-LUC 1E2-A2 (Dijkema R et al (1998) J Steroid Biochem Mol Biol, 64:147-56). The cells were cultured with charcoal-treated supplemented defined bovine calf serum from Hyclone (Utah, USA) in Dulbecco's Modified Eagles Medium/Nutrient Mixture F-12 (DMEM/HAM F12 in ratio 1:1) from Gibco (Paisley, UK).

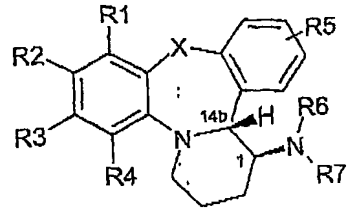
The antiprogestagenic activity of a test compound was determined by the inhibition of the transactivation via the progesterone receptor-B of the enzyme luciferase in the presence of 1 nM Org 2058 ((16α)-16-ethyl-21-hydroxy-19-norpregn-4-ene-3,20-dione) and compared with the reference antiprogestagen Org 31710 ((6βa,11β,17β)-11-[4-(dimethylamino)phenyl]-4',5'-dihydro-6-methylspiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one), and set at 100%. Agonistic ligands do not inhibit transactivation of luciferase activity induced by 0.1 nM Org 2058, whereas strong and weak antiprogestagens can inhibit transactivation dependent on the dose level used.

Progestagenic active compounds with an EC50 between 10000 and 100nM were identified for the compounds of experiment 1, 3, 5, 9, 10, 12, 14, 15, 16, 17, 18, 27, 28, 30, 31, 36, 37, 39, 40, 42A, 43 and 44. Compounds of experiments 11, 13, 21, 24, 29, 38, 45 and 46 showed an EC50 between 100 and 10 nm, whereas compounds of experiments 6, 7, 8, 13(1S14bR), 19, 20, 22, 23, 25, 26, 38B, 41 and 42 B showed an EC50 < 10 nM. The intrinsic activity relative to Org 2058 was in all compounds tested > 10%.

Anti-progestagenic active compounds with an EC50 between 10000 and 100nM were identified for the compounds of experiment 7, 9, 10, 13, 14, 15, 18, 21, 29, 32, 33, 34, 35, 38, 39, 41, 42A and 45. Compounds of experiments 7 and 22(1S,14bR) showed an EC50 between 100 and 10 nm, whereas compound of experiment 13(1S,14bR) showed an EC50 < 10 nM. The intrinsic activity relative to Org 31710 was in all compounds tested > 15%.

Claims

1. A compound according to general formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein
R1, R3, R4 and R5 independently can be selected from H, halogen, (1-4C)alkyl, OH, O(1-4C)alkyl, S(1-4C)alkyl or OC(O)(1-4C)alkyl,
R2 is H, halogen, NO_2, NR11R12, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, OH, O(1-4C)alkyl, S(1-4C)alkyl or OC(O)(1-4C)alkyl,
R6 is H, C(Y)R15, C(O)OR16, C(S)NR17 or (1-6C)alkyl,
R7 is H or (1-4C)alkyl, (2-4C)alkenyl or (2-4C)alkynyl, all optionally substituted with one or more halogen atoms,
R11 and R12 independently can be selected from H, (1-4C)alkyl, (2-4C)alkenyl or (2-4C)alkynyl, (1-6C)alkoxycarbonyl, (1-4C)alkylsulfonyl, (6-10C)arylsulfonyl,
R15 is H or (1-6C)alkyl, (2-4C)alkenyl or (2-4C)alkynyl , (6-10C)aryl, 1,4-bisaryl, amino(1-4C)alkyl, hydroxy(1-4C)alkyl, carboxy(1-4C)alkyl, all optionally substituted with one or more halogen atoms,
R16 is (1-6C)alkyl, optionally substituted with one or more halogen atoms,
R17 is (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl or (3-6C)cycloalkyl, all optionally substituted with one or more halogen atoms,
X=O, S, CH2 or NR18,
Y=O, S, or NH and
R18 is H or (1-4C)alkyl.

2. The compound according to claim 1 wherein
R2 is H, halogen, NO_2, NR11R12 and
R11 and R12 independently can be selected from H, (1-6C)alkoxycarbonyl, (1-4C)alkylsulfonyl or (6-10C)arylsulfonyl.

3. The compound according to claim 1 or 2 wherein
R1 and R5 are H and
R3 and R4 are selected from H or halogen.

4. The compound according to claims 1-4 wherein X=O, S or CH_2.

5. The compound according to claims 1-4 wherein

R6 is H or C(Y)R15 and

R15 is H or (1-4C)alkyl, optionally substituted with one or more halogen atoms.

6. The compound according to claims 1 -5 wherein

X=O or CH_2

R2 is H, halogen or NO_2

R15 is (1-2C)alkyl, optionally substituted with one or more halogen atoms.

7. The compounds according to claims 1-6 wherein

R11 is H and

R12 is (1-6C)alkoxycarbonyl, (1-4C)alkylsulfonyl or (6-10C)arylsulfonyl.

8. The compound according to claims 1-7 wherein

R2 is H

R3 is halogen

R15 is methyl, optionally substituted with 1-3 halogen atoms

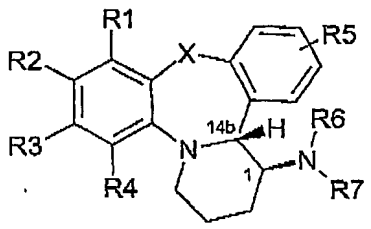
Y=O or S.

9. The compound according to claims 1-8 wherein R4 is H and/or X=O.

10. The compounds of any of the claims 1-9 for use in therapy.

Abstract

The present invention provides compounds according to general formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R1, R3, R4 and R5 independently can be selected from H, halogen, (1-4C)alkyl, OH, O(1-4C)alkyl, S(1-4C)alkyl or OC(O)(1-4C)alkyl,

R2 is H, halogen, NO_2, NR11R12, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, OH, O(1-4C)alkyl, S(1-4C)alkyl or OC(O)(1-4C)alkyl),

R6 is H, C(Y)R15, C(O)OR16, C(S)NR17 or (1-6C)alkyl,

R7 is H or (1-4C)alkyl, (2-4C)alkenyl or (2-4C)alkynyl, all optionally substituted with one or more halogen atoms,

R11 and R12 independently can be selected from H, (1-4C)alkyl, (2-4C)alkenyl or (2-4C)alkynyl, (1-6C)alkoxycarbonyl, (1-4C)alkylsulfonyl, (6-10C)arylsulfonyl,

R15 is H or (1-6C)alkyl, (2-4C)alkenyl or (2-4C)alkynyl , (6-10C)aryl, 1,4-bisaryl, amino(1-4C)alkyl, hydroxy(1-4C)alkyl, carboxy(1-4C)alkyl, all optionally substituted with one or more halogen atoms,

R16 is (1-6C)alkyl, optionally substituted with one or more halogen atoms,

R17 is (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl or (3-6C)cycloalkyl, all optionally substituted with one or more halogen atoms,

X=O, S, CH2 or NR18,

Y=O, S, or NH and

R18 is H or (1-4C)alkyl.